Annals of Clinical and Analytical Medicine
Original Research

The role of presepsin in predicting neonatal sepsis in cases of preterm premature membrane rupture

Preterm premature membrane rupture

Savaş Özdemir[1], Fatih Şahin[1], Gül Özel Doğan[2]
[1] Department of Obstetrics and Gynecology, Prof. Dr. Cemil Tascıoglu City Hospital
[2] Department of Gynecology and Obstetrics, Şişli Hamidiye Etfal Hospital, Istanbul, Turkey

Abstract
Aim: In this study, our aim was to evaluate the predictive value of presepsin (P-SEP) for neonatal sepsis in pregnant women with preterm premature rupture of the membranes (PPROM).
Material and Methods: The study included 20 pregnant women between the ages of 18 and 40 who presented with PPROM between the 24th and 37th weeks of pregnancy. The control group consisted of a total of 40 pregnant women, confirmed by last menstrual period and early ultrasound examinations, between the 24th and 37th weeks of pregnancy. In our study, samples were collected from both maternal and fetal umbilical cords in the PPROM group and from maternal and fetal cord blood in the control group. Presepsin levels were analyzed in the laboratory using an ELISA kit.
Results: No statistically significant relationship was found between maternal presepsin, fetal presepsin levels, and clinical data and laboratory assessments of the pregnant women.
Discussion: There is no relationship between presepsin levels and neonatal sepsis.

Keywords
Presepsin, Neonatal Sepsis, ELISA

DOI: 10.4328/ACAM.21927 Received: 2023-08-31 Accepted: 2023-10-06 Published Online: 2023-10-14 Printed: 2023-10-15 Ann Clin Anal Med 2023;14(Suppl 3):S334-337
Corresponding Author: Savaş Özdemir, Department of Obstetrics and Gynecology, Prof. Dr. Cemil Tascıoglu City Hospital, Istanbul, Turkey.
E-mail: savasozdemirdr@hotmail.com P: +90 212 314 55 55
Corresponding Author ORCID ID: https://orcid.org/0000-0003-3028-5804
This study was approved by the Ethics Committee of Istanbul Health Sciences University Prof. Dr. Cemil Tascioglu Clinical Research (Date: 2021-10-11, No: 329)

Introduction

Newborn sepsis is a significant cause of morbidity and mortality, particularly in premature infants [1]. The mortality rate can reach up to 70% in very low birth weight infants (birth weight < 1500 g) [2]. Beyond being a life-threatening condition, sepsis can lead to long-term complications in survivors and significantly impair the neurophysiological development of the brain [3, 4]. Given that the disease can rapidly progress to septic shock and multiple organ dysfunction syndrome, early diagnosis is crucial for improving survival. Unfortunately, diagnosing sepsis in newborns can be challenging. Blood culture is the gold standard for diagnosing sepsis, but results typically take at least 48-72 hours, and false-negative results cannot be ignored in cases of early-onset sepsis [5]. While various markers for sepsis have been identified, the quest for the optimal sepsis biomarker is still ongoing. Among these, C-reactive protein (CRP) lacks consistent specificity in distinguishing inflammatory conditions. Procalcitonin (PCT) has the advantage of rising more rapidly and appears to be more specific for bacterial infections [6]. Presepsin (P-SEP) is a fragment of soluble CD14 subtype (sCD14-ST), released as an acute response from monocytes and macrophages to microbial infection. Clinically, the aim is to identify newborns at high risk for early-onset sepsis before the onset of clinical symptoms and reduce the need for prophylactic antibiotic treatment [7]. In this study, our goal was to evaluate the predictive value of presepsin for neonatal sepsis in pregnant women with preterm premature rupture of the membranes (PPROM).

Material and Methods

The study was conducted at Sariyer Hamidiye Etfal Education and Research Hospital and included 20 pregnant women between the ages of 18 and 40 who presented with PPROM between the 24th and 37th weeks of pregnancy during the years 2020-2021. The control group consisted of a total of 40 pregnant women, confirmed by last menstrual period and early ultrasound examinations, between the 24th and 37th weeks of pregnancy. Pregnant women with a history of chronic diseases such as maternal systemic infection, hypertension, diabetes mellitus, or autoimmune diseases, those with clinical chorioamnionitis, those with polyhydramnios detected in ultrasound, multiple pregnancies, uterine malformations, and those with meconium-stained amniotic fluid were excluded from the study.

To determine presepsin levels, 1 mL of blood sample was collected into tubes containing ethylenediaminetetraacetic acid (EDTA). Plasma samples for presepsin were centrifuged at 3000 rpm for 5 minutes and stored at -80°C before analysis. Presepsin was measured using the PATHFAST immunoassay analyzer (Mitsubishi Chemical Medience Co.; Tokyo, Japan), a chemiluminescent enzyme immunoassay for the quantitative measurement of presepsin concentration. Monoclonal and polyclonal antibodies recognizing presepsin were used in the test. Presepsin concentration can be determined within 17 minutes using PATHFAST. In our study, samples were collected from both maternal and fetal umbilical cords in the PPROM group and from maternal and fetal cord blood in the control group. Presepsin analysis was performed using the presepsin ELISA kit in the Special Development Laboratory (Özel Gelişim Laboratuvarı). Diagnosis of neonatal sepsis was based on the Töller Scoring System [8], which combines clinical (hypotonia, bradycardia, apnea, respiratory distress, hepatomegaly, poor peripheral circulation, abdominal distension, and changes in skin color) and laboratory (elevated white blood cell count and low platelet count, metabolic acidosis, and immature/total neutrophil ratio) parameters. Each parameter is assigned a score from 0 to 3. If the total score is greater than 10, a clinical sepsis diagnosis is made.

The study was carried out with the permission of Istanbul Health Sciences University Prof. Dr. Cemil Tascioglu Clinical Research Ethics Committee (Date: 2021-10-11, Decision No: 329). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was conducted using SPSS 15.0 for Windows software. Descriptive statistics included counts and percentages for categorical variables, and for numerical variables, means, standard deviations, minimum, maximum, and medians were reported. Group comparisons for proportions were performed using the Chi-square test. Independent group comparisons for numerical variables were conducted using the Student t-test when the assumption of normal distribution was met and the Mann-Whitney U test when it was not met. Relationships between numerical variables were examined using Spearman's Correlation Analysis due to the non-parametric nature of the data. Associated factors were explored using Linear Regression Analysis. The alpha significance level was set at $p < 0.05$.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Mothers with early membrane rupture had a statistically significantly lower gestational age compared to the control group, shorter time until delivery, and a higher rate of normal spontaneous delivery (p=0.048, p=0.020, p=0.004, respectively). The findings are summarized in Table 1.

In pregnant women with early membrane rupture, there was no statistically significant difference in hemoglobin (Hb), hematocrit (Hct), white blood cell count (WBC), C-reactive protein (CRP), and presepsin levels compared to the control group. Similarly, among the babies of the groups described earlier, there was no statistically significant difference in Hb, Hct, WBC, CRP, and presepsin levels. The findings are summarized in Table 2.

Statistically significant relationships were not found between maternal presepsin and infant presepsin levels and the clinical data and laboratory assessments of pregnant women (Table 3). Multivariate Linear Regression Analysis based on variables with $p < 0.250$ in univariate analyses to examine the relationships between maternal and infant presepsin levels, did not identify any significant factors.

Discussion

In our study, there was no relationship found between neonatal sepsis and presepsin levels in preterm mothers with premature rupture of the membranes (PROM) compared to preterm mothers

without membrane rupture. Early diagnosis and treatment of sepsis are fundamental for improving survival. Currently, no single biomarker, such as white blood cell count (WBC), procalcitonin (PCT), C-reactive protein (CRP), or interleukin-6 (IL-6), which are widely used in clinical practice, can serve as an ideal biomarker for sepsis [9]. CD14, a glycoprotein expressed in monocytes and macrophages, serves as a receptor for bacterial lipopolysaccharides (LPS) and plays a role in activating the proinflammatory signaling cascade as part of the innate immune system. CD14 exists in two forms: membrane-bound (mCD14) and soluble (sCD14). Soluble CD14 subtype (sCD14-ST), also known as presepsin, significantly increases during the progression of sepsis cascades [9]. In a study, C-reactive protein (CRP), one of the other sepsis markers, had limited diagnostic potential in the early stages of sepsis due to delayed hepatic synthesis and the presence of other inducing factors independent of infection. Furthermore, CRP levels at admission were found to be similar in newborns with positive and negative blood cultures suspected of early-onset sepsis [10]. The use of procalcitonin (PCT), one of the most commonly used markers for sepsis, is limited because PCT levels can physiologically rise up to 48 hours after birth [11]. While the diagnostic efficiency of

Table 1. Demographic and Clinical Data of Pregnant Women.

		PROM Group Mean±SD Min-Max (Median)	Control Group Mean±SD Min-Max (Median)	P
Age		27.6±7,1	28.6±6.0	0.615*
		16-41 (25.5)	16-39 (28.5)	
Gravida		2.40±1.50	2.75±1.45	0.332
		1-6 (2)	1-6 (2)	
Parity		1.10±1.02	1,15±0,93	0.831
		0-3 (1)	0-3 (1)	
Abortion		0.20±0.52	0,45±0,83	0.258
		0-2 (0)	0-3 (0)	
Gestational Age		36.9±2.6	38,1±2,9	0.048
		30-41 (37)	29-41 (39)	
Digital Examination Dilatation		1.20±1.15	1,20±2,38	0.154
		0-3 (1)	0-9 (0)	
Digital Examination Effacement (%)		29,50±20,12	20,00±32,28	0.098
		0-80 (30)	0-90 (0)	
Fever		36,3±0,2	36,3±0,3	0.626*
		36-36,8 (36,3)	36-36,7 (36,25)	
Pulse		75,8±5,2	74,0±7,2	0.371*
		67-88 (76)	63-86 (74,5)	
Systolic Blood Pressure		114,9±8,0	120,8±19,0	0.583
		100-140 (113)	100-170 (116)	
Diastolic Blood Pressure		71,5±8,8	74,9±10,5	0,229
		60-100 (70)	62-100 (72)	
Time to Delivery		26,1±53,1	13,9±26,5	0.020
		4-240 (11,5)	1-120 (4)	
Mode of Delivery n (%)	CS	4 (20,0)	13 (65,0)	0.004#
	NSD	16 (80,0)	7 (35,0)	
Infant Hospitalization Duration		5,80±10,52	2,85±0,81	0,717
		1-46 (2,5)	2-4 (3)	

*Student t Test **Mann-Whitney U Test # Chi-square test

Table 3. Relationship between Presepsin and Clinical-Laboratory Data.

N=40	Maternal- Presepsin		Newborn- Presepsin	
	R	p	r	P
B- Presepsin	0,443	0,004		
Age	-0,119	0,466	-0,128	0,431
Gravida	-0,282	0,078	-0,283	0,076
Parity	-0,304	0,056	-0,267	0,096
Abortus	-0,106	0,513	-0,15	0,355
Gestational Age	0,234	0,146	0,151	0,352
Digital Examination Dilatation	0,128	0,431	0,243	0,131
Digital Examination Effacement (%)	0,006	0,971	0,163	0,315
Fever	0,027	0,867	-0,027	0,868
Pulse	0,018	0,913	0,207	0,199
Blood Pressure	-0,05	0,758	-0,036	0,825
Time to Delivery	0,031	0,849	0,159	0,328
Infant Hospitalization Duration	0,225	0,163	0,137	0,399
Mother				
Hb	-0,238	0,139	-0,254	0,114
Hct	-0,241	0,134	-0,213	0,186
WBC	-0,15	0,354	-0,042	0,796
CRP	0,225	0,164	0,215	0,183
Infant				
Hb	-0,104	0,524	0,102	0,533
Hct	-0,248	0,122	0,082	0,614
WBC	0,046	0,779	-0,16	0,324
CRP	0,1	0,539	0,095	0,559

Table 2. Laboratory Data for Pregnant Women and Infants in Both Groups.

	Mother			Infant		
	PROM Group Mean±SD Min-Max (Median)	Control Group Mean±SD Min-Max (Median)	p	PROM Group Mean±SD Min-Max (Median)	Control Group Mean±SD Min-Max (Median)	P
Hb	11,5±1,3	11,3±0,8	0,449*	18,2±1,4	18,0±1,9	0,635*
	9,1-14,2 (11,95)	9,7-12,8 (11,2)		14-20 (18,2)	14,9-21,9 (18)	
Hct	34,9±3,3	33,8±2,4	0,243*	53,1±4,2	53,0±6,5	0,927*
	28-42 (35)	29-37 (33,8)		43-58 (54)	44-70 (53)	
WBC	12,8±5,5	12,8±5,6	0,957	16,9±4,4	18,4±5,0	0,415
	6-28 (12,5)	7-29 (11,5)		8,9-27 (17)	11-29 (16,5)	
CRP	5,35±5,78	5,80±5,23	0,784	3,45±1,10	3,33±1,27	0,854
	1-28 (4)	1-21 (4,5)		1-5 (4)	0,6-5 (4)	
Presepsin	426,8±543,0	305,2±247,7	0,482	516,6±704,5	354,5±397,6	0,516
	100,9-2069 (215,55)	157,8-1286 (233,55)		137,5-3187 (249,55)	155,1-1975 (232,6)	
Sepsis n (%)	0	0		0	0	

these markers may increase when combined, identifying a single early-onset sepsis marker with high sensitivity and positive predictive value (PPV) would benefit clinical practice. Consensus on pediatric sepsis definitions has limited accuracy for term newborns and is not suitable for premature infants. The primary reason is that organ dysfunction, the fundamental diagnostic criterion, is rarely considered in the newborn literature, and it remains unclear how newborns should be screened for organ dysfunction [12]. Previously published data have supported the use of presepsin in the diagnosis of early-onset sepsis and have demonstrated similar or higher diagnostic accuracy compared to other inflammatory markers [13]. Therefore, incorporating presepsin into clinical practice may help prevent false-positive sepsis diagnoses, limiting newborns' exposure to antimicrobial drugs, their side effects, and invasive procedures [14].

The limitation of this study include limited number of registered newborns, and the quantitative heterogeneity of the studied subgroups could affect the precision of statistical analysis. Secondly, the absence of positive blood culture samples and sepsis in our cohort limits the predictive value of presepsin. Based on our data, we recommend that the performance of presepsin be prospectively investigated in larger cohorts and in heterogeneous groups in the future.

Conclusion

There is no relationship between presepsin levels and neonatal sepsis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding: *None*

Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Rose E. Pediatric Fever. Emerg Med Clin North Am. 2021; 39(3): 627-39.
2. Yildiz A, Sahin F. Role of Pregnancy Associated Plasma Protein (PAPP-A) and Free Human Chorionic Gonadotropin (B-HCG) in Predicting Adverse Pregnancy Outcomes. 2016; İKSST Derg 8(1):20-9.
3. Gan MY, Lee WL, Yap BJ, Seethor STT, Greenberg RG, Pek JH, et al. Contemporary Trends in Global Mortality of Sepsis Among Young Infants Less Than 90 Days: A Systematic Review and Meta-Analysis. Front Pediatr. 2022: 3;10:890767.
4. Gravina G, Ardalan M, Chumak T, Nilsson AK, Ek JC, Danielsson H, et al. Proteomics identifies lipocalin-2 in neonatal inflammation associated with cerebrovascular alteration in mice and preterm infants. iScience. 2023; 27; 26(7): 107217.
5. Küng E, Unterasinger L, Waldhör T, Berger A, Wisgrill L. Cut-off values of serum interleukin-6 for culture-confirmed sepsis in neonates. Pediatr Res. 2023; 93(7): 1969-74.
6. Boscarino G, Migliorino R, Carbone G, Davino G, Dell'Orto VG, Perrone S, et al. Biomarkers of Neonatal Sepsis: Where We Are and Where We Are Going. Antibiotics (Basel). 2023: 26; 12(8):1233.
7. Kim CJ. Current Status of Antibiotic Stewardship and the Role of Biomarkers in Antibiotic Stewardship Programs. Infect Chemother. 2022; 54(4): 674-98.
8. Sofouli GA, Tsintoni A, Fouzas S, Vervenioti A, Gkentzi D, Dimitriou G. Early Diagnosis of Late-Onset Neonatal Sepsis Using a Sepsis Prediction Score. Microorganisms. 2023; 17; 11(2): 235.
9. Velissaris D, Zareifopoulos N, Karamouzos V, Karanikolas E, Pierrakos C, Koniari I, et al. Presepsin as a Diagnostic and Prognostic Biomarker in Sepsis. Cureus. 2021;13(5):e15019.
10. De Rose DU, Perri A, Auriti C, Gallini F, Maggio L, Fiori B, et al. Time to positivity of blood cultures could inform decisions on antibiotics administration in neonatal early-onset sepsis. Antibiotics (Basel). 2021; 10(2):123.
11. Wang SY, Yu JL. Diagnostic value of procalcitonin in neonatal early-onset sepsis. Zhongguo Dang Dai Er Ke Za Zhi. 2020; 22(4): 316-22.
12. McGovern M, Giannoni E, Kuester H, van den Hoogen A, Bliss JM, Koenig JM, et al. Challenges in developing a consensus definition of neonatal sepsis. Pediatr Res. 2020; 88(1):14-26.
13. Maddaloni C, De Rose DU, Santisi A, Martini L, Caoci S, Bersani I, et al. The emerging role of presepsin (P-SEP) in the diagnosis of sepsis in the critically ill infant: a literature review. Int J Mol Sci. 2021; 22:12154.
14. Poggi C, Lucenteforte E, Petri D, De Masi S, Dani C. Presepsin for the diagnosis of neonatal early-onset sepsis: a systematic review and meta-analysis. JAMA Pediatr. 2022;176(8):750-8.

How to cite this article:
Savaş Özdemir, Fatih Şahin, Gül Özel Doğan. *The role of presepsin in predicting neonatal sepsis in cases of preterm premature membrane rupture. Ann Clin Anal Med 2023;14(Suppl 3):S334-337*

This study was approved by the Ethics Committee of Istanbul Health Sciences University Prof. Dr. Cemil Tascioglu Clinical Research (Date: 2021-10-11, No: 329)